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(54)【発明の名称】 ベブチド被覆インプラントおよびその製造方法

## (57)【要約】

本発明は、試験管内では、個々の場合において、適当な生体材料の組織一体化を完成すると考える細胞種の付着を主に刺激し、同時に、試験管内において、そのプロセスに反する細胞種の付着をよくは刺激することのない、合成された、細胞または組織選択性RGDペプチドによる被覆により、生体材料、特にインプラントの生体機能付加の可能性を記載する。

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$\text{>-(CH}_2\text{)}_n\text{-[NH-CO-(CH}_2\text{)}_n\text{]-P-NH-CO-CH=CH}_2\text{ A}$  (ii)

$\text{--A A 8 G}$

$\text{O-CH}_2\text{-O-CH}_2\text{-CH}_2\text{-O-CH}_2\text{-CH}_2\text{-NH}_q\text{-CO-(CH}_2\text{)}_r\text{-NH-CO-CH=CH}_2\text{ A}$  (iii) A

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$\text{>-CH}_2\text{-CH}_2\text{-SH G}$  (ia)



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rthoplasty, 63 " Annual Meeting of the American Academy of Orthopaedic Surgeons, Atlanta; Haddad 1996 The Journal of Bone and Joint Surgery C 78-B #546 549 ; Collinge , 1996 Pin Tract Infections) B

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Tyr(Y)	~								
Ser(S)	Z								
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Lys(K)		V							
DPhe(f)	D	t	F	j	Å				
Pro(P)		V							
Leu(L)		Q							
Ile(I)	C	¥	Q						
Val(I)	o								
Glu(E)	O	^							
Thre(T)	g	§							
Ala(A)	A	j							
	i	a	j	D	RGD	L	y	v	E

RGD(Arg-Gly-Asp) A

GRGD(Arg-Gly-Asp) A

GRGDY(Arg-Gly-Gly-Asp-Tyr) A

RGDS(Arg-Gly-Asp-Ser) A

GRGDS(Arg-Gly-Gly-Asp-Ser) A

RGDF(Arg-Gly-Asp-Phe) A

GRGDF(Arg-Gly-Gly-Asp-Phe) A

V NRGDFK(Arg-Gly-Asp-DPhe-Lysine) A

V NRGDFKG(Arg-Gly-Asp-DPhe-Lys-Gly) B

b j D RGD L y v E

LDV(Leu-Asp-Val) A

LCTIPG(Leu-Glu-Thr-Ile-Pro-Gly) A

REDV(Arg-Glu-Asp-Val) A

IKVAV(Ile-Lys-Val-Ala-Val) A

YIGSRG(Tyr-Ile-Gly-Ser-Arg-Gly) A

LRE(Leu-Arg-Glu) A

PDSGR(Pro-Asp-Ser-Gly-Arg) A

DCEA(Asp-Gly-Glu-Ala) A

RYVVLPR(Arg-Tyr-Val-Val-Leu-Pro-Arg) B

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のため、本発明において始めて適用された、「Kevloc®」プロセス (EP 0 712 621)、

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 Ø Y v ' h A ❹

「Silicoater®」プロセス (DE-A 42 25 106) のように、本発明によるインプラ

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 1993 Analytical Biochem C 215 " 223 J A ' I [ ❻

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i ♫ h10p l j } Q ♩

† F E<sup>2</sup>m† F t E<sup>2</sup>m

a / " F E ♫

" MC3T3 H1 } E X E

" " F E ♫

BSA A &lt; F ♫

\_\_\_\_} E \_\_\_\_\_ I [ ♫-SMPB U - - ♫ ♫ - ♩

i ♫ m0 ° j } Q ♩

† F E<sup>2</sup>m

j † F Z o ♫ K v ♩

} F ' I [ H-SMPB U - - - ♀ % - - -  
 i ♀ h0 ° } Q ♀  
 † F ♀  
 † F E ♀  
 a / MC3T3 H1 } E X  
 " F E ♀  
 " / " F E ♀  
 PMMA ¥ ° MC3T3 H1 } RGD Y v ' h - - ♀ %  
 RGD Y v ' h Z ♀

E

a / " MRGDFK NH-CO- A N ♀ ^ C #ia A A N

[ g y v

a / " MRGDFK NH-CO- A N ♀ ^ C #ib A A N

[ g y # A

" / " MRGDFK NH-CO- A N ♀ ^ C #ib A A N

[ g y v

" / " MRGDFK NH-CO- A N ♀ ^ C #ia A A N

[ g y # A

} K \_\_\_\_\_ RGD Y v ' h - - PMMA PHEMA ¥ ° MC3T3 H1 L  
E F

† F RGD Y v ' h Z ♀  
 † F E ♀  
 a / " MRGDFKNH-CO- A N ♀ ^ C #ia A A N  
 [ g y v  
 " MRGDFK NH-CO- A N ♀ ^ C #ib A A N [  
 g y v # A  
 " / " MRGDFK NH-CO- A N ♀ ^ C #ib A A N

[ g y A

10 F X

L E E

† F RGD y v ' h Z }

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a / " ERGDEK NH-CO- A N      ^ Gilia A A N

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( ^ C fib A A N" / " ERGDEK NH-CO- A N [

— X " q RGD y v ' h - φ PMMA % †

X -BSA-SMPB ¥ ° MC3T3 H1 L E E

RGD y v ' h }

† F - }

} 12 F

a / " F 100 ° l y  $\Psi$   
 a " F  $\diamond$  n t  $\Psi$   
 0.1 ° l y  $\Psi$  " " F  $\Psi$   
 " / " F  $\Psi$

} 14 F \_\_\_\_\_ RGD y v ' h

N [ g y v ' h R  $\Psi$ PMMA  $\Psi$  ° MC3T3 H1 L E

¤  $\leftarrow$  B

100 ° AO ° l  $\Psi$  ° l X h z n t  $\Psi$

$\Psi$  °  $\pm$   $\mathbb{C}$  % L E

† F E 105nm  $\square$  fl Ø

} 15 F \_\_\_\_\_ RGD y v ' h

A N [ g y v ' h T  $\Psi$ PMMA  $\Psi$  ° MC3T3 H1 L

E  $\square$  E

100 ° AO ° l  $\Psi$  ° l X h z n t  $\Psi$

$\Psi$  °  $\pm$   $\mathbb{C}$  % L E

† F E 105nm  $\square$  fl Ø

} 16 F \_\_\_\_\_ RGD y v ' h

N [ g y v ' h R  $\Psi$ PMMA  $\Psi$  ° MC3T3 H1 L E

A  $\leftarrow$  '  $\square$  L E

100 ° l h z n t y v ' h Z x  $\Psi$

P ^ A  $\leftarrow$  ' P  $\square$  E

† F E 105nm  $\square$  fl Ø

} 17 F \_\_\_\_\_ RGD y v '  $\Psi$ RGDFKG NH-CO- A N [ g  $\Psi$ ia A

A N [ g y v ' h T  $\Psi$ PMMA  $\Psi$  ° MC3T3

H1 L E A  $\leftarrow$  '  $\square$  L E

†

P ^ A  $\leftarrow$  ' P  $\square$  E

† F E 105nm  $\square$  fl Ø













E - 0.7 2mm PMMA - Eplex Y7H A [ 50g A

Y Q O O P Y

^ N (MMA) n 68.6 MMA 29.4 TEGMA & tBPP) 1.5ml ^ <  
 A % E z S z -   
 ¥ d MMA < ' i A N [ g y v '   
 N [ g y v ' h P A Q A R n S   
 100 ° l " EMSO 0.2 J t @ v j n t » %   
 B # A C ¥ 2 J t @ v j -   
 L A e 0.1nM AnM A0nM A00nM A ° l 40 ° l -   
 ' h Z x " Ø E A Z x +   
 x [ g - £ - % B g p o   
 • BBS pH7.4 - ABS pH7.4 ~ S -   
 B

^ ' BBS pH7.4 BSA T Y '   
 C L x BBS pH7.4 I æ • Ø - '   
 ' u   
 y v ' h n t a f - 2 J t @ v j   
 n t -   
 - \$ ~ A } E X V I MC3T3 H1 n Heermeie   
 r C995 Cells and Materials C E09 321 - j a L   
 ¥ ° t B   
 MC3T3 H1 L E A O Postar48- E G v AGD y   
 v ' h - MMA < ' i " / 8,000 En - A   
 25 C ... CO2 1 - C L x [ g %   
 " ' BBS C pH7.4 - æ x B   
 t E Sandegren B 1984 CJ. Immunol. Methods C 67 " B7   
 9 388 - j } ' ~ A K " E A Z ' w   
 - [ [ < Ø -   
 O L A N BGD y v B ^ C



{ **■**  
Y V ' h ♀ <sup>25</sup> fi ¥ ° ■4A X e  
X X ' [ **■** 7 <sup>3</sup> mm j ~ A R ' " Ø **■**  
E A  
♀ ' □ i A . » 50 15 " C  
  
L x [ g A E C I 50 " C L **■**  
A ~ x E C I - 50 24 C L **■**  
» a A R ' ~ L X e **■**  
a. Kevloc®プロセス (Heraeus Kulzer GmbH、ヴェールハイム、ドイツ) :  
Kevloc®プライマー溶液を、薄く塗布し、室温で3分間インキュベートした。  
次に、Kevloc®ボンド溶液を、同様に薄く塗布し、炉内にて180°Cで20分間活性





\_\_\_\_\_D

RGD y v ' h E c % A L **Z**  
 < x ~ s ~ MC3T3 H1 L £350,000  
 E cm ) A q g z j x £50,000 L  
 En " 50,000,000 < cm j A A N [ **g**  
 A N [ g y **PMMA** c ' i a s **Z**  
 t A { E R **g**  
 6.0Abs j ^ e & z < L E ^ e s A < **g**  
 Ø ^ A A N **PMMA** c ' i D **g**  
 B E < x ~ - **Z**.  
 • Ø **Z**  
 " " A A N **g** I I **PMMA** c ' **g**  
 " A t " **g** z < 6.0Abs j "  
 < L 5.5Abs j " Ø ^ A **g** 17) B ...  
 < x ~ ~ " Ø ^ A L  
 6.5Abs j v " " Ø **Z**  
 - E " " A EGD y v ' h Ø C v  
 c A I E D c t } **g**  
 Ø - " " " Ø B - E A L E ^ **g**  
 F  
 E C e O I  
 L # " c % ~ ~ " x ' **Z**  
 e O " " L " Ø - E E **g**  
 E - L " " A **g** " " ~ c **g**  
 Ø B

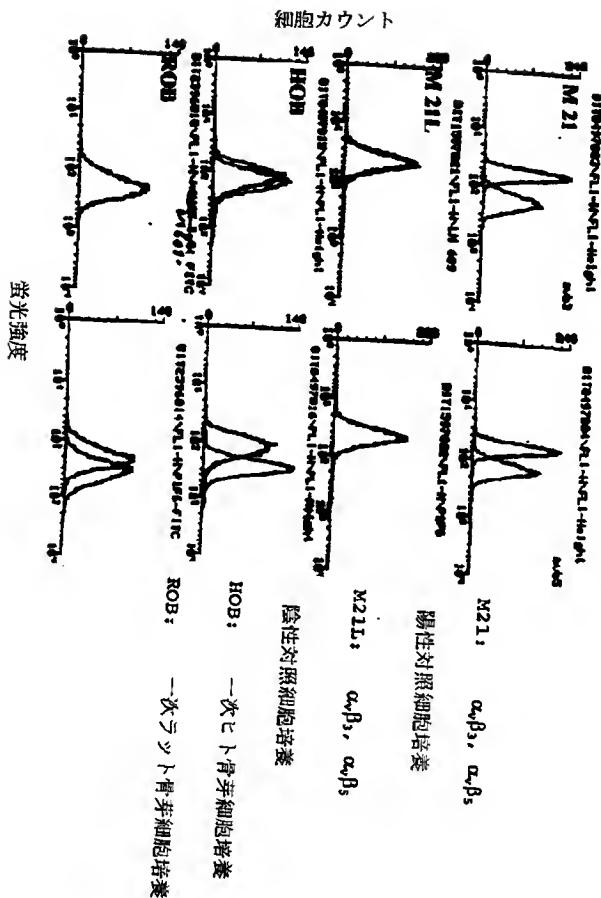


図 1

細胞付着率 [%]

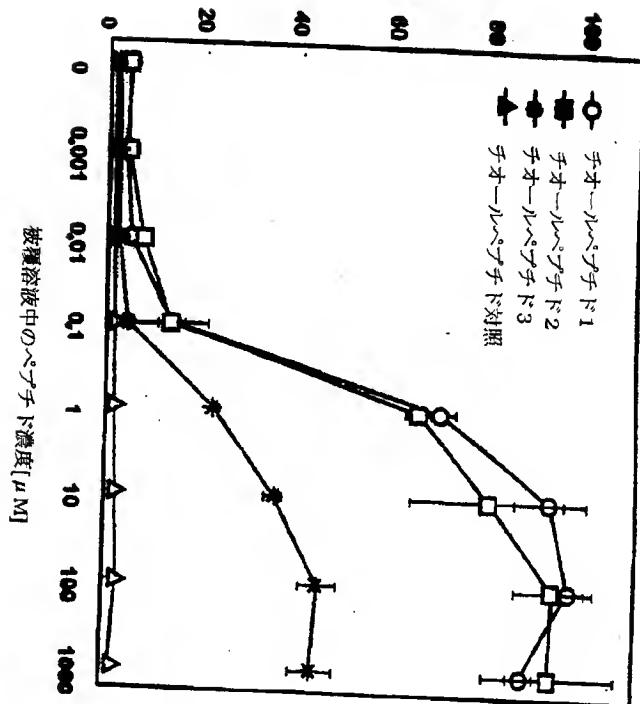


図 2

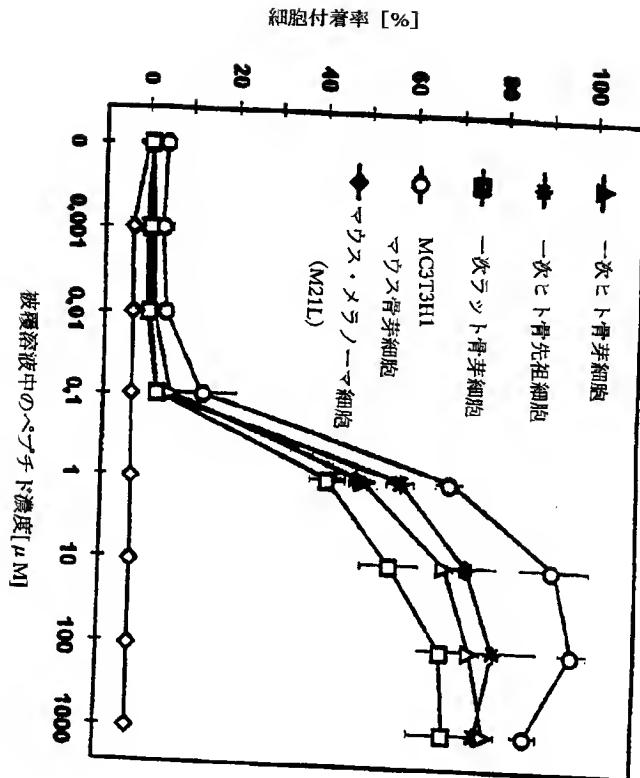


図 3

細胞付着率 [%]

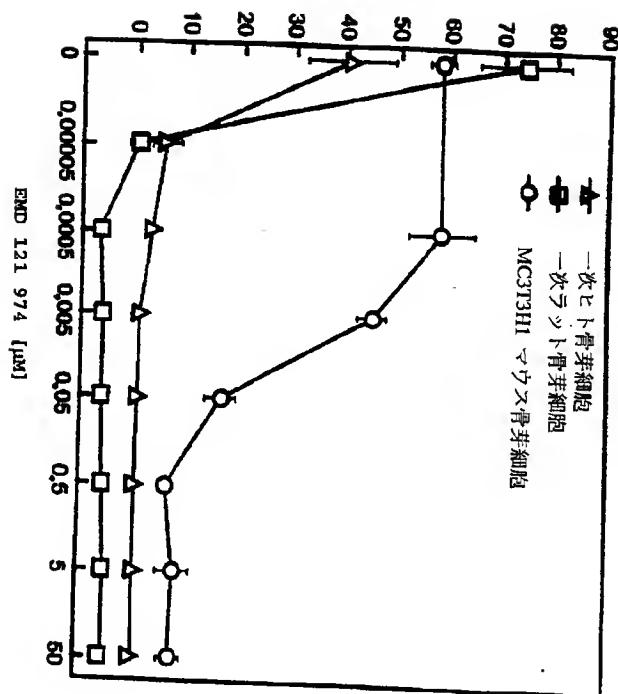


図 4

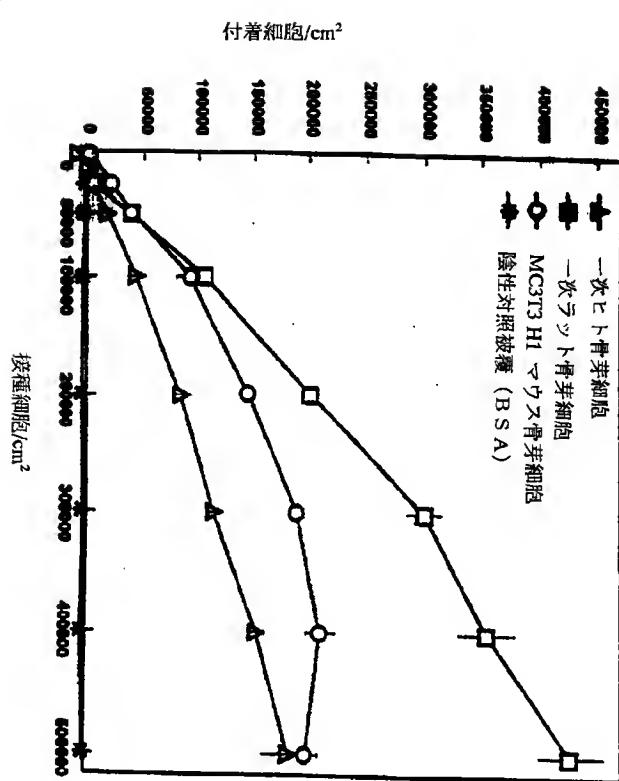


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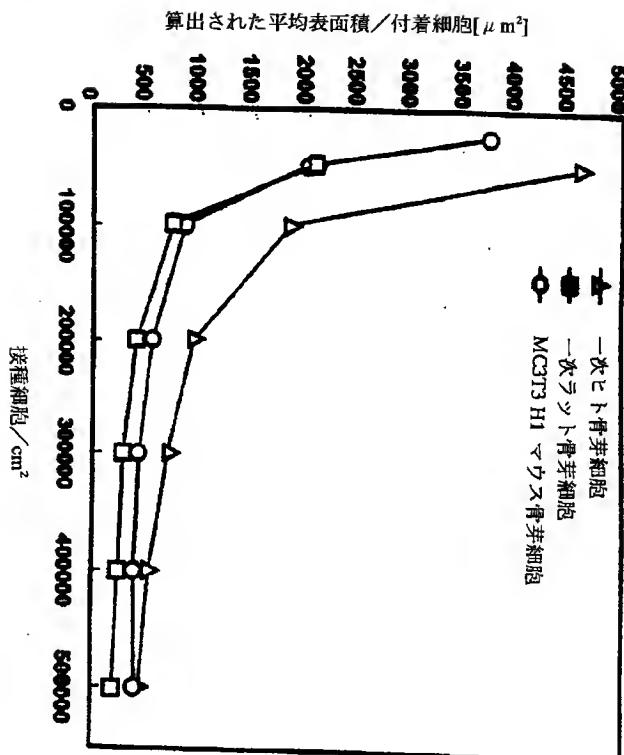


図 6

細胞付着率 [%]

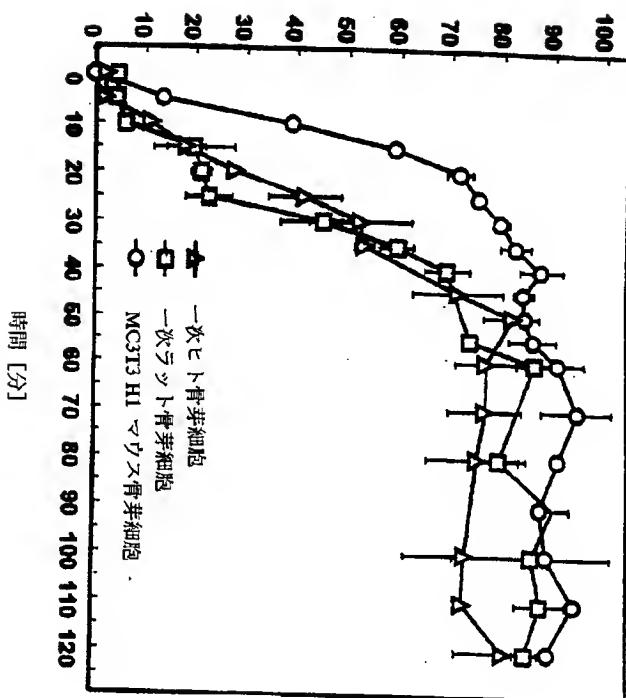


図 7

細胞付着率 [%]

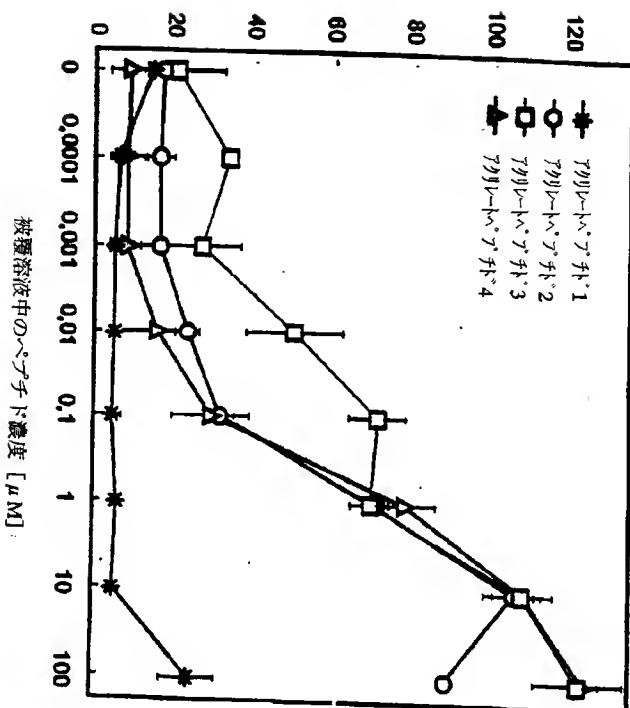


図 8

細胞付着率 [%]

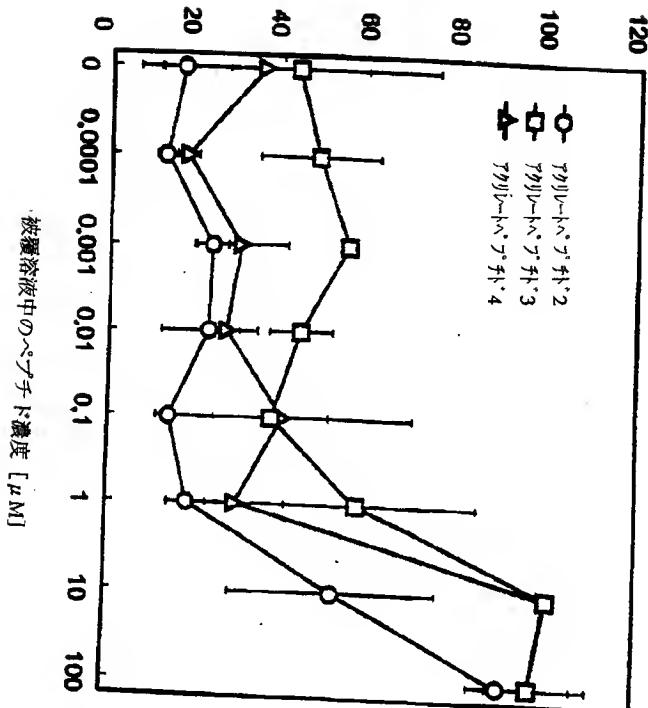


図 9

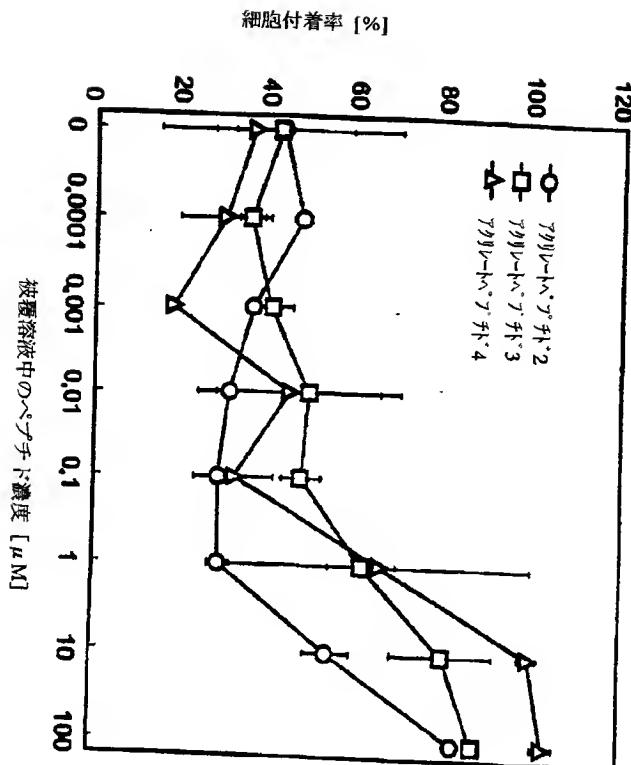


図 10

Y } E

最大細胞付着率 [%]

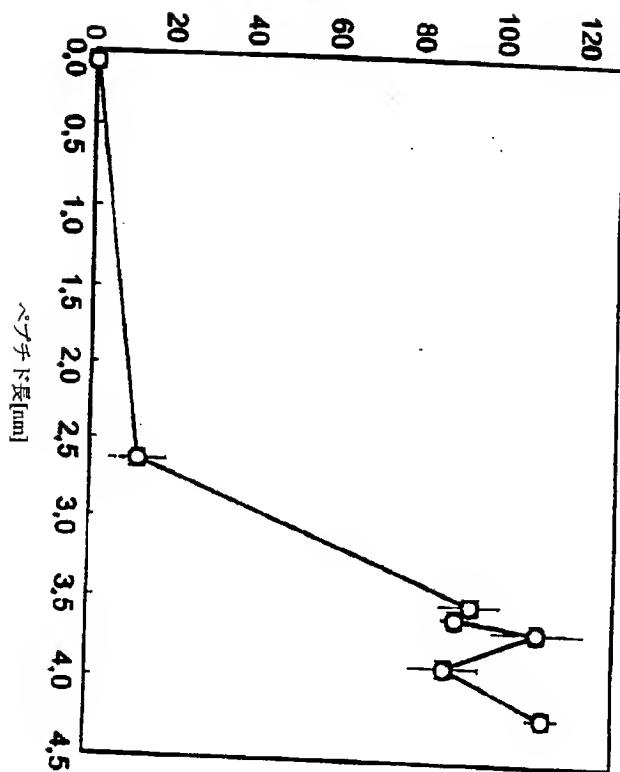


図 11

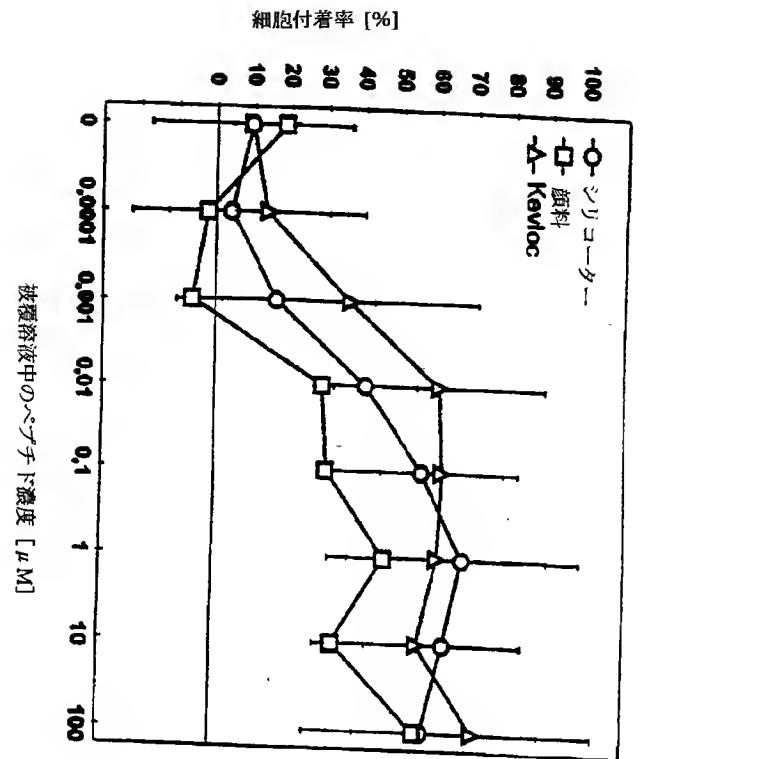


図 1 2

## 細胞カウント

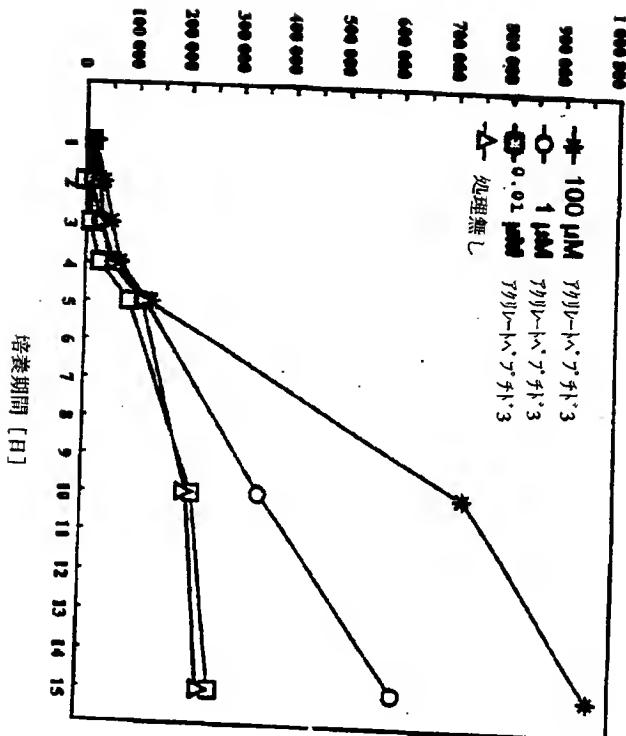


図 13

Y } 图

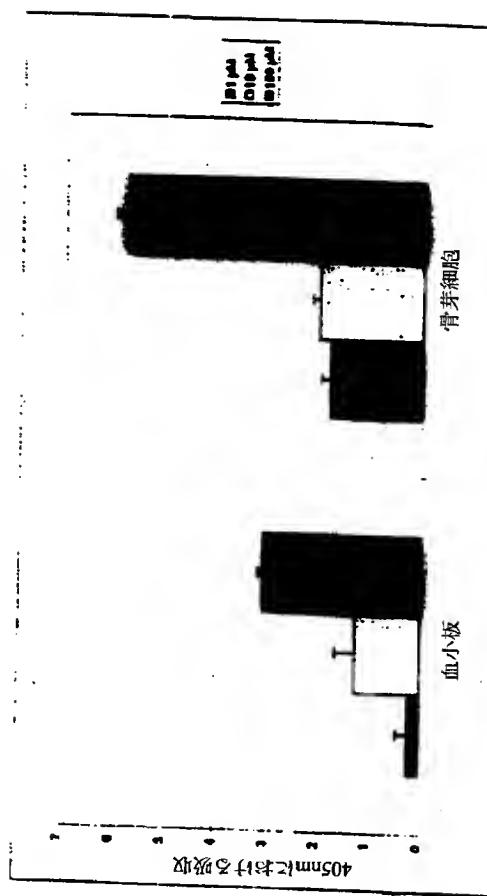


图 14

Y } R

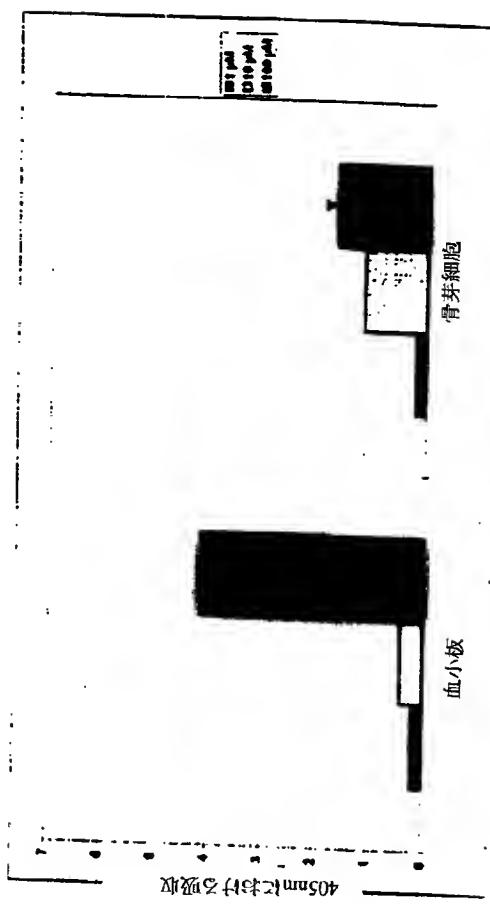


図 15

Y } □

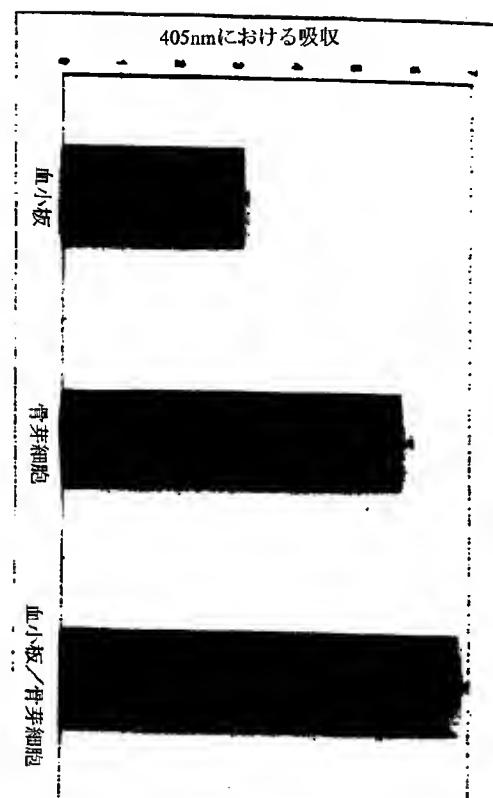


図 16

Y } Y

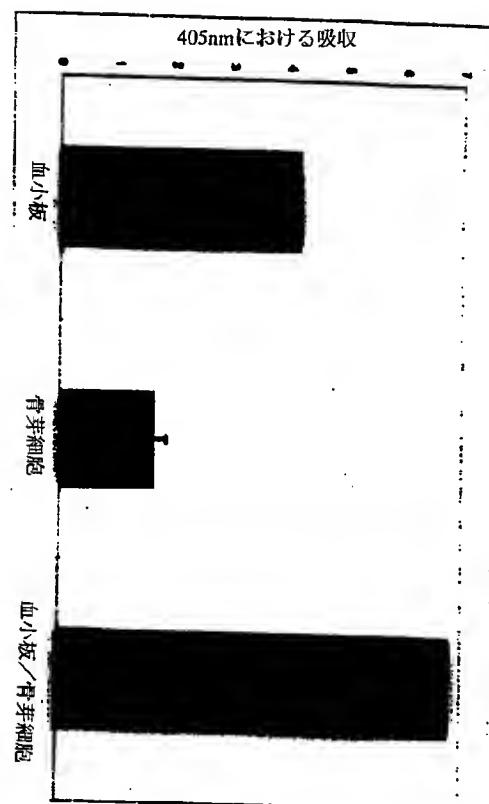


図 17

Y + 2

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 98/02753

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6 A61L27/00 C07K17/06		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 6 A61L C07K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the International search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 00047 A (UNIV CASE WESTERN RESERVE) 9 January 1992 see claims 1-3,42-44	1,2,7,8, 11-14
A	HIRANO Y ET AL.: "Synthesis and cell attachment activity of bioactive oligopeptides: RGD, RGDS, RGDV, and RGDT" JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, vol. 25, no. 12, December 1991, pages 1523-1534, XP002090255 cited in the application see page 1528, paragraph 4 - page 1529, paragraph 1	1,2,7,8, 11-14
<input type="checkbox"/> Further documents are listed in the continuation of box C.		<input type="checkbox"/> Patent family members are listed in annex.
<p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"U" document which may throw doubts on priority (claims) or which is cited to establish the publication date of another citation or other special reason (not specified)</p> <p>"D" document referring to an oral disclosure, see, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>		
Date of the actual compilation of the International search	Date of mailing of the International search report	
19 January 1999	01/02/1999	
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patenttaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3216	Authorized officer Heck, G	

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat'l Application No  
PCT/EP 98/02753

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9200047 A	09-01-1992	AU 8286491 A	23-01-1992

